REMARKS

Applicants and counsel sincerely thank Examiner Dunston and Examiner Low for granting a personal interview on September 29, 2009, which was attended by the undersigned, Applicants' European counsel (Dr. Graf von Stosch) and lead inventor Dr. Ingmar Hoerr. An interview summary has been made of record by the Examiner.

With this RCE, Applicants present previously pending claims 31-36 (claim 31 being amended herein) and respectfully request further consideration of the patentability of these claims over the sole remaining ground of rejection. Supplementing the record, Applicants herewith submit the Third Declaration of Dr. Ingmar Hoerr ("Hoerr III").

The claimed subject matter is drawn to a pharmaceutical composition which contains a modified mRNA. The mRNA is modified to contain an increased content of Guanine/Cytosine (G/C) units relative to the corresponding wild-type mRNA ("G/C enrichment"). It is specified that the modified mRNA encodes a human tumor antigen. The G/C enriched mRNA is stabilized in relation to the corresponding wild-type mRNA. Support for this added recitation in claim 31 is found, e.g., at paragraphs [0019] and [0020] of the specification.

The rejection of record cites to the combined teachings of Felgner et al., Zhou et al, Adema et al, Nagata et al, and Fomsgaard to find that the claimed subject matter would have been obvious within the meaning of 35 U.S.C. 103. Applicants request reconsideration in light of the following discussion and further submission of evidence (as well as the evidence already contained in the record of this application).

Initially, the combined teachings of Felgner et al. and Zhou et al. do not suggest enrichment of the G/C content of an mRNA. As noted previously, Felgner suggests various nucleic acid modifications (e.g. col. 12, lines 15-30) but notably does not suggest G/C enrichment. Zhou likewise does not suggest G/C enrichment.

The rejection takes the position that it would have been obvious – from Adema *et al*, Nagata *et al* and Fomsgaard – to "optimize" the codons of ***any*** sequence for expression in a

human cell (including the sequence of a human tumor antigen). Official Action of 12/23/08, page 7; see also, Official (Advisory) Action of 5/15/09, pages 3 and 5.

In response, the invention as claimed would not have been obvious for at least the following reasons: 1) the inventors surprisingly found that an mRNA which is G/C enriched is more stable than the corresponding wild-type mRNA; and 2) at the time of the invention, it would not have been obvious to enrich the G/C content of an mRNA encoding a human tumor antigen for expression in a human system.

As to the first point, Dr. Hoerr's declaration provides further evidence confirming the disclosure of the specification that G/C enrichment unexpectedly stabilizes mRNA. The effect is seen in different mRNAs and was truly surprising in view of the state of the art at the time the present invention was made. Hoerr III, ¶¶ 2-5. [1]

As to the second point, Applicants stress the importance of viewing the "state of the art" as it would have been understood by persons actually working in the art at the time the invention was made, avoiding hindsight.[2] Contemporaneous literature suggests that persons working in the

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[1] The discovery that stability of mRNA could be enhanced by G/C-enrichment is part of the inventive subject matter as a whole under 35 USC 103, and can be analogized to discovering a problem which those of skill in the art at the time of the invention had failed to appreciate (i.e. that mRNAs encoding human genes can be sequence-modified for improved stability and prolonged expression in human cells). A long line of authority supports finding non-obviousness where a "problem" in the art went unrecognized. See, e.g. *In re Antonson*, 124 USPQ 132, 133 (CCPA 1959)("... it must not be lost sight of, as pointed out by the Supreme Court in *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 67, 43 S.Ct. 322, 67 L.Ed. 523 that the inventive act which entitles an applicant to a patent resides as well in the discovery of the source of trouble as in the application of the remedy"); *In re Sponnoble*, 167 USPQ 237, 243 (CCPA 1969) ("[A] patentable invention may lie in the discovery of the source of a problem ... This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 USC 103.").

[2] See, e.g. *In re Linnert*, 135 USPQ 307, 311 (CCPA 1962) ("Viewed in the light of appellants' specification, the solution to the problem ... may seem obvious over the combined teaching teachings of the references. Such a hindsight analysis, however, is not allowed by 35 U.S.C. 103 which requires a comparison of the prior art and the invention *at the time the invention was made*") (emphasis in original; citations omitted); *KSR International Co. v.*

art at the time of the invention would have seen no reason to "optimize" the codons of a human gene for expression in a human cell. The prior art – including the cited references to Nagata *et al* and Fomsgaard – was directed to the specific problem of enhancing the expression of poorly-expressed pathogenic, non-human genes in human cells in order to improve vaccine efficacy against pathogens.

Before addressing Nagata *et al* and Fomsgaard in detail, Applicants note that Adema *et al* disclose a nucleotide sequence encoding gp100 and suggest variants of that sequence based on the degeneracy of the genetic code. While any degenerate sequence could potentially be "envisioned" from such a disclosure (Advisory Action, page 4, line 5), Adema's generalized disclosure does not suggest the use of G/C- enriched molecules, and does not suggest any benefits associated with using G/C- enriched molecules. Hoerr III, ¶11. Adema *et al* supplies no motivation to modify the disclosure of Felgner et al. and/or Zhou to enrich the G/C content of an mRNA encoding a human tumor antigen.

The Nagata *et al* reference reports on experiments using subsequences from bacterial and protozoal pathogens. They adapted the codon usage of those subsequences to the codon usage of mammalian cells and tested their expression and induction of cytotoxic T lymphocytes (CTL). There is no suggestion in Nagata et al. that optimizing codons (which in the context of Nagata is "humanizing" of codons) would be relevant when seeking to express human genes in human cells. Hoerr III, ¶17. In fact, Nagata co-authored a review article published in 2000 (one year later than the cited Nagata et al. paper, reference 19 in the review) which is suggestive of the non-obviousness of the present invention. Koide et al, "DNA Vaccines", Jpn. J. Pharmacol., 83: 167 (2000) (copy attached as Exhibit D to Hoerr III). In the discussion of codon "optimization" on page 171, 2d column, the review states:

> "Although many bacteria have been targets of DNA vaccines, significant progress has been made with Mycobacterium tuberculosis. One of

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Teleflex, Inc., 82 USPQ 2d 1385, 1397 ("A fact finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant on *ex post* reasoning").

> the reasons seems to be the bias in codon usage in M. tuberculosis genes. Surprisingly, the bias, unlike any other bacteria examined, is comparable to that of Mus musculus and Homo Sapiens (17), suggesting that the codon-optimization described above could be unnecessary for the construction of DNA vaccines against M. tuberculosis."

This statement reflects that, according to Nagata and his co-authors who were actually working with "codon optimization" experiments at the relevant time prior to the present invention, "codon optimization" was not considered to be relevant or necessary in the case of genes already having a mammalian codon bias. Hoerr III, ¶ 18. Please also note that codon optimization does not necessarily increase G/C content. Hoerr III, ¶ 10.

Fomsgaard's disclosure is concerned with improving the expression of pathogenic HIV genes, which were known to be poorly-expressed in human cells, to increase their potential utility as anti-HIV vaccines. The HIV genes are expressed in a Rev-dependent manner. Fomsgaard also mentions that rare codons exist in HIV genes. See, e.g., Fomsgaard, page 1.

Dr. Hoerr makes several points in connection with Fomsgaard's disclosure. There is clearly no disclosure in Fomsgaard (or in the Haas et al. (1996) paper cited by Fomsgaard) to optimize codons in non-HIV-1 genes. In fact, the Haas et al. paper, a copy of which is provided with Dr. Hoerr's declaration, suggests that the need for "codon re-engineering" is applicable in the case of "proteins that are poorly expressed in mammalian cells." Hoerr III, ¶¶ 11-13.

Fomsgaard's suggestion to codon-optimize a gene to minimize "ribosomal pausing" would not have been recognized by a skilled artisan as being relevant to expression of human genes in human cells. Hoerr III, ¶ 14.

While it was logical to seek to improve the expression of poorly-expressed pathogenic HIV genes in human cells by modifying the pathogenic genes to utilize codons which are more prevalent in human cells, Fomsgaard provides no suggestion to introduce human codon usage into a human gene, such as a gene encoding a human tumor antigen. Hoerr III, ¶ 15. Fomsgaard's disclosure which relates to rendering expression of HIV genes Rev-independent has

no applicability to the present invention, since (insofar as is currently known) human tumor antigens are not dependent on HIV Rev protein for their expression. Hoerr III, ¶ 16.

The disclosures of Nagata et al. and Fomsgaard suggest to "optimize" codon usage in the context of preparing DNA vaccines to immunize humans against pathogenic organisms. These references do not suggest that a human gene would need to be optimized/humanized to introduce human codon usage. Indeed, assuming a need to optimize human genes for expression in human cells would have been counterintuitive, since the skilled person would have believed that millions of years of evolution would have fine-tuned human gene expression in human cells far more efficiently than could be achieved by designing man-made, synthetic nucleic acid sequences. Hoerr III, ¶ 19. Moreover, no correlation between codon usage and expression level in human genes was understood at the time of the present invention. *Id.*

Lastly, the cited references to Fomsgaard and Nagata et al. disclose the codon optimization of DNA, not mRNA, and do not suggest to provide a modified mRNA in the isolated environment of a pharmaceutical composition, as claimed. Hoerr III, ¶ 20.

Based on the foregoing, the record is submitted to amply support the patentability of the current claims. Favorable action on claims 31-36 is respectfully solicited.

Applicants submit herewith the fee for an RCE and a five-month extension of time (measured from the expiration of the period for filing of an appeal brief). If any further fees are due with this response, please charge our Deposit Account No. 03-2775, under Order No. 22122-00009-US1 from which the undersigned is authorized to draw.

Dated: December 22, 2009

Respectfully submitted,

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Enclosure: Third Declaration of Ingmar Hoerr (Hoerr III), with attachments